Received: 10 October 2021 | Revised: 22 November 2021 | Accepted: 26 November 2021

DOI: 10.1111/ajt.16907

ORIGINAL ARTICLE

Effectiveness of T cell–mediated rejection therapy: A systematic review and meta-analysis

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Funding information
Paul I Terasaki Research Fund.

The effectiveness of T cell–mediated rejection (TCMR) therapy for achieving histological remission remains undefined in patients on modern immunosuppression. We systematically identified, critically appraised, and summarized the incidence and histological outcomes after TCMR treatment in patients on tacrolimus (Tac) and mycophenolic acid (MPA). English-language publications were searched in MEDLINE (Ovid), Embase (Ovid), Cochrane Central (Ovid), CINAHL (EBSCO), and Clinicaltrials.gov (NLM) up to January 2021. Study quality was assessed with the National Institutes of Health Study Quality Tool. We pooled results using an inverse variance, random-effects model and report the binomial proportions with associated 95% confidence intervals (95% CI). Statistical heterogeneity was explored using the I^2 statistic. From 2875 screened citations, we included 12 studies (1255 participants). Fifty-eight percent were good/high quality while the rest were moderate quality. Thirty-nine percent of patients (95% CI 0.26–0.53, I^2 77%) had persistent ≥Banff Borderline TCMR 2–9 months after anti-rejection therapy. Pulse steroids and augmented maintenance immunosuppression were mainstays of therapy, but considerable practice heterogeneity was present. A high proportion of biopsy-proven rejection exists after treatment emphasizing the importance of histology to characterize remission. Anti-rejection therapy is foundational to transplant management but well-designed clinical trials in patients on Tac/MPA immunosuppression are lacking to define the optimal therapeutic approach.

KEYWORDS
clinical research/practice, graft survival, immunosuppression/immune modulation, immunosuppressive regimens, kidney (allograft) function/dysfunction, kidney transplantation/nephrology, rejection: antibody-mediated (ABMR), rejection: T cell mediated (TCMR)

Abbreviations: ABMR, antibody-mediated rejection; BPAR, biopsy-proven acute rejection; CI, confidence intervals; *dn*DSA, *de novo* donor-specific antibody; MECIR, methodological expectations of cochrane intervention reviews; MPA, mycophenolic acid; NIH, National Institutes of Health; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, randomized controlled trials; Tac, tacrolimus; TCMR, T cell–mediated rejection.

1 | INTRODUCTION

Biopsy-proven acute rejection (BPAR) is an immune breakthrough event in transplant patients on maintenance immunosuppression. Subclinical and clinical BPAR are prognostically significant as they predict death-censored graft loss and BPAR is an accepted endpoint for clinical trials.[1–6] The majority of BPAR in the first year is due to T cell–mediated rejection (TCMR) with Banff Borderline being the most common grade of rejection in patients on modern immunosuppression with tacrolimus (Tac) and mycophenolic acid (MPA).[7] These early TCMR events can lead to chronic alloimmune injury including development of *de novo* donor-specific antibody (*dn*DSA) and chronic active antibody-mediated rejection (ABMR), or chronic active TCMR, both of which independently lead to graft loss.[7–10] There are currently no effective therapies for chronic active ABMR or chronic active TCMR, suggesting the key to improving long-term graft prognosis is to achieve remission of early TCMR events to prevent activation of irreversible chronic inflammatory pathways.

Evaluating histological outcomes after early TCMR therapy is critical to defining the rates of remission and overall therapeutic effectiveness. While 60%–70% of clinicians rely on graft functional markers to define BPAR resolution,[11,12] serum creatinine is very insensitive with only an AUC 0.59 for detecting BPAR.[13] There is a dearth of evidence evaluating histologic persistence of BPAR after anti-rejection therapy for TCMR. Indeed a systematic review of BPAR treatment from 1997 to 2015 identified only five studies that examined the response to anti-rejection therapy and these studies used graft function, not histology.[14] To better understand the effectiveness of current anti-rejection therapy for achieving histological remission of TCMR in patients on modern maintenance Tac/MPA-based therapy we systematically identified, critically appraised, and summarized the available literature since 2015 on the incidence and outcomes of persistent TCMR after treatment of an index Banff Borderline or greater TCMR event that occurred on Tac/MPA-based therapy.

2 | METHODS

This review was conducted in accordance with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines,[15] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[16] We a priori registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO [CRD42021258622]). The review questions were: "What is the histological course of TCMR (inclusive of Banff Borderline) following anti-rejection therapy in kidney transplant patients on Tac/MPA therapy?" and "What is the impact of TCMR on outcomes in kidney transplant patients on Tac/MPA therapy?"

2.1 | Search strategy

A knowledge synthesis librarian designed a literature search strategy for MEDLINE (Ovid) and this was peer reviewed by another independent librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist.[17] The search strategy (Table S1) was adapted for Embase (Ovid), Cochrane Central (Ovid), CINAHL (EBSCO), and ClinicalTrials.gov (NLM). We limited our search to studies published from 2015 to January 2021 in the English language. Our decision to limit to studies since 2015 was because reports of Tac/MPA-based therapy were uncommon before then and a previous systematic review, published in 2016 whose search considered studies up to October 2015,[14] showed that none of the included studies would provide evidence for this review. All citations were imported and de-duplicated in EndNote (version X9).

2.2 | Selection criteria

We imported the de-duplicated citations in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) and two independent systematic reviewers screened the citations using a two-stage sifting approach to review the title/abstract and full-text articles of relevant citations. We documented the number of ineligible citations at the title/abstract screening stage, and both the number and reasons for ineligibility at the full-text article screening stage. The two reviewers resolved any disagreements through discussion or involvement of a third reviewer, as needed. Where necessary, we contacted authors and 10 study authors responded with clarifications, study information, and line level data for the meta-analysis where applicable (listed in the Acknowledgments).

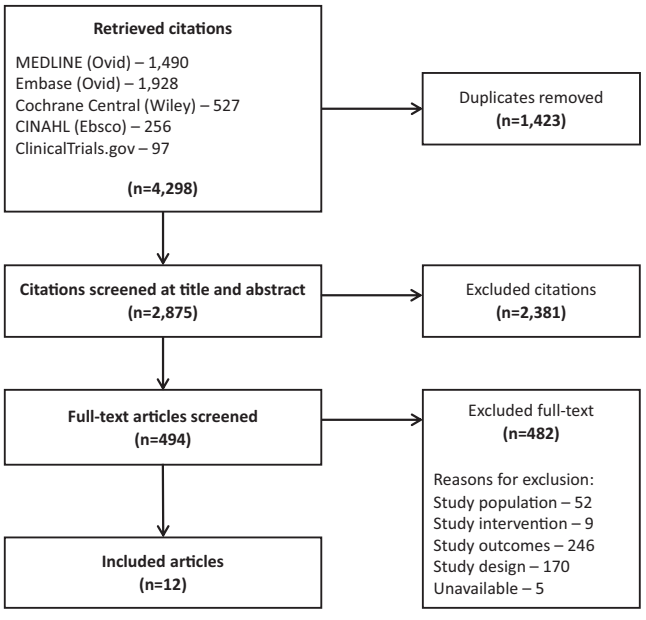


FIGURE 1 Modified PRISMA flow chart

TABLE 1 Summary characteristics of the included studies

Study (country)	Study period	Study type (patients, transplant)	Initial BPAR diagnosis (index biopsy type, time posttransplant)
Chandran 2021[24] (USA)	2014–2018	Single-center RCT 30 adult	≤borderline[a] Protocol, 6–12 month
Hoffmann 2021[29] (Canada)	2012–2018	Multicenter prospective 97 pediatric	≥borderline Protocol, 45 days (IQR:37–78) Indication, 365 days (IQR:118–400)
Chen 2021[25] (Taiwan)	2007–2013	Single-center retrospective 68 adult	≥borderline Protocol, 2 years
Mehta 2020[30] (USA)	2013–2019	Single-center prospective 415 adult	≤borderline[b] Protocol, 3 month (92 ± 31 days)
Cherukuri 2019[26] (USA)	2013–2018	Single-center prospective 294 adult	≥Banff 1A Protocol and indication, 0–5 month
Hoffman 2019[28] (USA)	2013–2018	Single-center prospective 192 adult	≥Banff1A Protocol, 3 month Indication in first year
Bouatou 2019[8] (France)	2004–2018	Single-center prospective 256 adult	≥Banff 1A Indication, 3.52 month (IQR 2.11–11.87)
Friedewald 2019[27] (USA)	2011–2014	Multicenter prospective (CTOT08) 253 adult	≥borderline Protocol, 2–6, 12 and 24 month
Nankivell 2019[31] (Australia)	2012–2017	Single-center retrospective 551 adult	≥borderline Protocol and indication
Seifert 2018[33] (USA)	2008–2014	Single-center consecutive retrospective 103 pediatric	≥borderline Protocol, 3 or 6 month
Zhu 2018[34] (Canada)	2004–2013	Single-center retrospective 26 adult	≥borderline Protocol, 3–6 month
Naumnik 2017[32] (Poland)	2010–2013	Single-center prospective 17 adult	≥Banff 1A Protocol, 3 month

Abbreviations: ABMR, antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy; IFTA+i, interstitial fibrosis and tubular atrophy with inflammation; IQR, inter-quartile range; RCT, randomized controlled trial.

[a]Graft inflammation defined as Banff Borderline *or* interstitial inflammation (i or ti1-2) without tubulitis, t0.

[b]Stratified by Banff Borderline definition 1997 and 2005.

[c]Mixed ABMR/TCMR included with TCMR outcomes.

We included studies with ≥10 adult and/or pediatric kidney transplant patients with acute kidney rejection confirmed histologically (BPAR) or based on the BANFF Grade. We excluded multiple organ transplants except for kidney-pancreas transplants. The patients must have been on Tac/MPA-based therapy to be eligible for inclusion. We excluded trial registrations with no published outcomes and studies not reporting on outcomes of relevance to this review.

TCMR therapy	Time to next biopsy	Persistent BPAR diagnosis (follow-up biopsy type)	Other relevant outcomes (follow-up duration)
Tocilizumab 8 mg/kg every 4 weeks × 6 versus placebo	6 months	≤borderline[a] Protocol	DSA, ABMR, eGFR, death-censored graft loss, death 12 month
Pulse IV/oral steroids (variable)	49 days median (IQR 40–56)	≥borderline Protocol and indication	NA 1.3 ± 0.7 year
Methylprednisolone 500 mg IV × 3 days	5 years	≥borderline Indication	ABMR, eGFR, death-censored graft loss 7 years
Untreated	9 months	≥borderline Protocol and indication	IFTA, DSA, eGFR, death-censored graft loss 6 years (median 45 months)
Banff 1A/B: Methylprednisolone 250 mg IV × 3 days and prednisone 5 mg maintenance. Banff≥2A and steroid resistant: thymoglobulin (max 6 mg/kg)	9 months	≥Banff 1A Protocol and indication	DSA, IFTA, IFTA+i, graft loss 4 years
Banff 1A/B: Methylprednisolone 250 mg IV × 3 days and prednisone 5 mg maintenance. Banff≥2A and steroid resistant: thymoglobulin (max 6 mg/kg)	9 months	≥Banff 1A Protocol and indication	DSA, eGFR, death-censored graft loss, death 5 years (mean 59, range 43–68 month)
Banff ≥1A: Methylprednisolone 500 mg IV × 3 days and oral prednisone taper up to 3 months to reach 10 mg daily. Steroid resistant: thymoglobulin (7.5 mg/kg)	3 months	≥Banff 1A and chronic active TCMR Protocol	DSA, ABMR, eGFR, death-censored graft loss Median 7.07 years (IQR, 3.24–11.23)
Per site practice (variable)	8 weeks	≥borderline[c] Protocol	ABMR, IFTA, eGFR decline from 4–24 month
Methylprednisone, thymoglobulin, IVIG, increased maintenance immunosuppression (variable)	2.2 ± 2.9–3.2 ± 3.3 months	≥borderline Protocol and indication	DSA, ABMR, IFTA, eGFR, death-censored graft loss, death 5 years
No therapy; enhanced immunosuppression; IV pulse steroids, occasionally thymoglobulin (variable)	3 months and variable	≥borderline[c] Protocol and indication	DSA, ABMR, eGFR, death-censored graft loss, death 5 years
Borderline: prednisone 5 mg daily ≥Banff 1A: Methylprednisolone 250 mg IV × 1 then prednisone 1 mg/kg until 5 mg	6–9 months	≥borderline Protocol	ABMR, eGFR, death-censored graft loss and death 5 years
Banff 1A: increased maintenance immunosuppression Banff 2B: Methylprednisolone 500 mg IV × 3 days and thymoglobulin	9 months	≥Banff 1A Protocol	DSA 12 month

2.3 | Outcomes

The primary outcomes were persistent and recurrent TCMR. Persistent TCMR was defined as biopsy-proven ≥Banff Borderline TCMR on subsequent biopsy after treatment of an index ≥Banff Borderline TCMR event. Recurrent TCMR was defined as biopsy-proven ≥Banff Borderline TCMR on follow-up biopsy, with an intervening normal biopsy showing histological resolution of rejection

TABLE 2 Study quality assessment

Study	Country	Research objective stated	Study population specified	Study participation rate ≥50%	Study subjects from the same population	Justification provided for sample size	Exposures measured before outcome	Sufficient study time frame
Bouatou 2019	France	Yes	Yes	Yes	Yes	No	Yes	Yes
Chandran 2020	USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen 2021	Taiwan	Yes	Yes	Yes	Yes	No	Yes	Yes
Cherukuri 2019	USA	Yes	Yes	Yes	Yes	No	Yes	Yes
Friedewald 2019	USA	Yes	Yes	Yes	No	No	Yes	Yes
Hoffman 2019	USA	Yes	Yes	Yes	Yes	No	Yes	Yes
Hoffmann 2020	Canada	Yes	Yes	Yes	Yes	No	Yes	Yes
Mehta 2020	USA	Yes	Yes	Yes	Yes	No	Yes	Yes
Nankivell 2019	Australia	Yes	Yes	Yes	Yes	No	Yes	Yes
Naumnik 2017	Poland	Yes	Yes	Yes	Yes	No	Yes	Yes
Seifert 2018	USA	Yes	Yes	Yes	Yes	No	Yes	Yes
Zhu 2018	Canada	Yes	Yes	Yes	Yes	No	Yes	Yes

Abbreviations: CD, cannot determine; NA, not applicable; NR, not reported.

after treatment of an index ≥Banff Borderline TCMR event. As we were unable to identify studies reporting ≥3 sequential biopsies with serial histological outcomes, recurrent TCMR was excluded from the analysis. Secondary outcomes were the development of *de novo* donor-specific antibodies (dnDSA) or antibody-mediated rejection (ABMR), graft loss (censored and not censored for death), mortality, Banff grades on follow-up biopsy, and persistent TCMR following an index Banff Borderline TCMR event that was not treated.

2.4 | Data extraction and study quality assessment

One reviewer extracted data from the included studies using Microsoft Excel 2016 spreadsheet and a second reviewer independently checked the extracted data for errors. We extracted publication details (name of first author, year of publication, name of journal), study details (country, region, period, funder, type, sample size), population characteristics (kidney donor, patient type, sex distribution, participants' age summaries, proportions of patients on Tac/MPA, initial BPAR type, indication for biopsy), information regarding interventions (treatment for BPAR), outcomes assessed (type and follow-up duration) and results (number analyzed and number with outcome). Two reviewers independently assessed study quality using the National Institutes of Health (NIH) study quality assessment tool for observational cohort and cross-sectional studies.[18] We judged a study to be of high quality if not lacking in any of the assessed domains, of good quality if lacking in one or two domains, of moderate quality if lacking in three to five domains, and of low quality if lacking in six or more domains. Disagreements were resolved through discussion or by involvement of a third reviewer, as needed.

2.5 | Data synthesis and analysis

We synthesized the characteristics of the included studies and the quality assessments in a tabular form and summarized them narratively. Where possible (when data from at least two studies are sufficiently statistically and clinically homogeneous), we conducted meta-analysis using an inverse variance, random-effects model, and reporting the binomial proportions (P) with associated 95% confidence intervals. We explored and quantified statistical heterogeneity of the pooled proportions, using the I^2 statistic.[19] Each study's proportions and associated standard error were calculated using double-arcsine transformation method before conducting meta-analysis.[20,21] The transformed summary proportion and associated confidence interval were converted back for ease of interpretation. We utilized R packages metafor[22] and meta[23] with metaprop function for the statistical analyses. We assessed publication bias for only one outcome that had enough included studies.

We conducted pre-specified subgroup analyses assessing the effect of study quality (high quality vs. moderate/low quality), funding (industry vs. non-industry), follow-up duration (≤1 year vs. >1 year), patient population (males vs. females), demographics (pediatric [≤18 years]) vs. adult (>18 years), BPAR type (TCMR vs. ABMR) and transplant type (kidney-only vs. kidney-pancreas). We also

Different levels of exposures measured	Consistent exposure measurement	Exposure assessed more than once	Consistent outcome measures	Blinding of outcome assessors	≤20% loss to follow-up	Confounder adjustment	Overall
NA	Yes	NA	Yes	Yes	Yes	NA	Good quality
NA	Yes	NA	Yes	Yes	Yes	NA	High quality
NA	Yes	NA	No	NR	Yes	NA	Moderate quality
NA	Yes	NA	No	NR	Yes	NA	Moderate quality
NA	Yes	NA	Yes	Yes	Yes	NA	Good quality
NA	Yes	NA	Yes	NR	Yes	NA	Good quality
NA	Yes	NA	No	NR	Yes	NA	Moderate quality
NA	Yes	NA	Yes	NR	No	NA	Moderate quality
NA	Yes	NA	Yes	NR	NA	NA	Good quality
NA	Yes	NA	Yes	NR	No	NA	Moderate quality
NA	Yes	NA	Yes	CD	Yes	NA	Good quality
NA	Yes	NA	Yes	NR	No	NA	Moderate quality

conducted post-hoc subgroup analyses on severity of TCMR (≥Banff Borderline vs. ≥Banff 1A), rejection type (clinical vs. subclinical), and definition of Banff Borderline (Banff 1997 Borderline vs. Banff 2005 Borderline definition).

3 | RESULTS

3.1 | Systematic review and study characteristics

From 2875 unique citations identified through our systematic literature search, 12 studies[8,24–34] (involving 1255 participants) met our eligibility criteria (Figure 1). The characteristics of these studies are summarized in Table 1. Half of the studies ($n = 6$) were from the United States of America (USA),[24,26–28,30,33] two studies were from Canada,[29,34] while one study each was from Australia,[31] France,[8] Poland,[32] and Taiwan.[25] There was one randomized controlled trial (RCT),[24] two multicenter prospective observational cohorts,[27,29] five single center prospective observational cohorts,[8,26,28,30,32] and four single-center retrospective cohorts.[25,31,33,34] Two studies reported receiving industry funding.[24,27] All studies involved both sexes (varying proportions) with 10 adult and two pediatric studies.[29,33] Study sample size ranged from 17 to 551 patients, and the overall study period was from 2004 to 2019. Patient population description differed slightly across the studies, with patients in three studies receiving kidney/pancreas transplants.[30,31,34] The proportion of deceased donor kidney transplants ranged from 31 to 82% in 10 studies and two studies had 100% deceased donors[32,34] (Table S2).

3.2 | Study quality

One study was high quality having satisfied all assessed study quality domains,[24] five studies were good quality having satisfied all but one or two study quality domains,[8,27,28,31,33] and the rest were moderate quality having satisfied all but three study quality domains.[25,26,29,30,32,34] None of the studies were low quality. Table 2 presents a summary of the study quality assessments.

3.3 | Index rejection event, immunosuppression, and treatment

The index BPAR event largely occurred within the first year with two studies reporting an index BPAR at 2 years posttransplant.[25,27] In terms of index rejection severity, four studies reported ≥Banff 1A,[8,26,28,32] six reported ≥Banff Borderline rejection,[25,27,29,31,33,34] and two studies reported tubulointerstitial inflammation ≤Banff Borderline by the Banff 2005 criteria.[24,30] Four studies defined borderline rejection with the Banff 1997 criteria requiring at least ≥i1 score.[26,29–31] The incidence of index subclinical BPAR was 30% and clinical BPAR was 16% when excluding studies with 100% index BPAR based on the inclusion criteria.[8,24] Maintenance steroids were used in seven cohorts,[24,25,27,31–34] not reported in one study,[29] and four studies did not routinely use steroids at index biopsy (three studies from one cohort)[8,26,28,30] (Table S3).

TCMR treatment consisted of variable doses and duration of pulse steroids, typically intravenous methylprednisolone 250–500 mg daily for 3 days and/or augmented maintenance immunosuppression. One trial randomized patients 1:1 with ≤subclinical Banff Borderline rejection

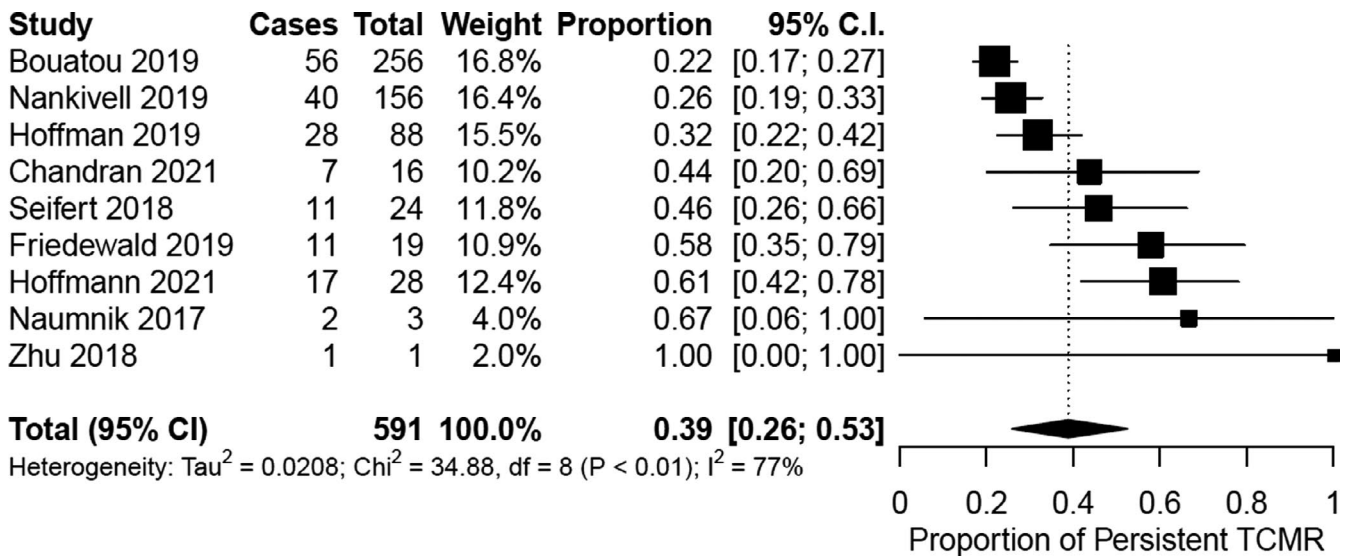


FIGURE 2 Forest plot for persistent ≥Banff Borderline rejection following treatment of ≥Banff Borderline rejection

to placebo versus tocilizumab 8 mg/kg monthly for 6 months.[24] There was heterogeneity in treatment approaches to subclinical versus clinical rejection and severity of the index rejection event. Subclinical Banff Borderline rejection was variably treated in five studies,[24,25,29,31,33] untreated in four studies (three studies from one cohort)[26,28,30,34] and not reported or not applicable in three studies (Table S2).[8,27,32]

3.4 | Persistent TCMR

Follow-up biopsies occurred within 2–9 months of the index BPAR event in 11 studies. One study[25] was excluded from the meta-analysis as the next biopsy occurred up to 5 years after the index BPAR. The primary outcome showed the pooled proportion of persistent ≥Banff Borderline was 0.39 (95% CI 0.26–0.53, I^2 77) after treatment of an index ≥Banff Borderline rejection (Figure 2). There was a higher proportion of persistent rejection in pediatric (0.54, 95% CI 0.32-0.74, I^2 9) relative to adult kidney transplant patients (0.32, 95% CI 0.20–0.45, I^2 68) and this finding remained stable across the different subgroup analyses. Furthermore when kidney-pancreas studies were excluded the findings remained stable with 42% of patients having persistent rejection on follow-up biopsy after treatment of an index ≥Banff Borderline rejection (0.42, 95% CI 0.28–0.56, I^2 0.81; Table 3).

The pooled proportion of persistent ≥Banff Borderline after treatment of ≥Banff 1A was 0.39 (95% CI 0.23–0.56, I^2 70; Figure 3). The pooled proportion of persistent ≥Banff Borderline after treatment of a subclinical ≥Banff Borderline was 0.46 (95% CI 0.28–0.65, I^2 66; Figure 4A) and 0.41 (95% CI 0.19–0.64, I^2 82; Figure 4B) after treatment of a clinical ≥Banff Borderline. While the index rejection severity and subclinical versus clinical rejection findings appeared stable, these subgroup analyses may have been confounded by the heterogeneous treatment approaches used. Finally, a sensitivity analysis was undertaken using only the Banff 1997 Borderline definition with a minimum i1t1 score. The pooled proportion of persistent ≥Banff 1997 Borderline after treatment of an index ≥Banff 1997 Borderline with a minimum i1t1 score was 0.41 (95%CI 0.11–0.76, I^2 92; Figure S1). In summary the proportion of persistent BPAR remained relatively stable across the different subgroup analyses comparing index rejection severity, subclinical versus clinical rejection, and the Banff 1997 versus Banff 2005 Borderline definitions (Table 3).

3.5 | Persistent TCMR following an initial Banff Borderline TCMR event that was not treated

Six studies consistently treated ≥Banff 1A rejection[8,25,26,28,32,34] and four multicenter studies had variable treatment per site practice.[27,29,31,33] One study did not treat subclinical Banff Borderline rejection[30] while another randomized half of subclinical Banff Borderline patients to placebo.[35] The pooled proportion of persistent ≥Banff Borderline after an untreated subclinical ≥Banff Borderline rejection event was 0.61 (95%CI 0.41–0.79, I^2 60; Figure 5).

3.6 | Development of ABMR, graft loss (censored and not censored for death), and mortality

The pooled proportion of ABMR after treatment of ≥Banff Borderline rejection was 0.02 (95% CI 0.00–0.10, I^2 73; Figure 6). Seven studies reporting graft loss demonstrated a pooled proportion of 0.29 (95% CI 0.03–0.66, I^2 98) and three studies showed a pooled proportion of 0.42 (0.00–0.95, I^2 98) for death. There was abbreviated and variable follow-up for ABMR and graft loss outcomes, ranging from 1 to 7 years (Table 1). These data should be interpreted with caution due to the wide confidence intervals, era effect in the Banff definition for ABMR,[36] and high study heterogeneity for graft loss and mortality. The overall findings of this study are summarized in Figure 7.

TABLE 3 Summary of results

Outcome	Subgroup	No. of studies	Population size	Pooled proportion (95% CI)	I^2 Statistic (%)
Persistent ≥Banff Borderline following treatment of ≥borderline rejection	Overall	9	591	0.39 (0.26–0.53)	77
	Pediatric	2	52	0.54 (0.32–0.74)	9
	Adult	7	539	0.32 (0.20–0.45)	68
	Outcome measure ≤1 year	8	435	0.42 (0.27–0.58)	79
	Outcome measure >1 year	1	156	0.26 (0.05–0.55)	—
	Industry-funded studies	2	35	0.51 (0.26–0.76)	0
	Non-industry-funded studies	7	556	0.35 (0.21–0.50)	77
	Kidney transplant-only	7	434	0.42 (0.28–0.56)	81
	Kidney-pancreas transplant	2	157	0.25 (0.00–0.64)	60
Persistent ≥Banff borderline following treatment of ≥Banff 1A rejection	Overall	8	428	0.39 (0.23–0.56)	70
	Pediatric	2	27	0.57 (0.33–0.79)	51
	Adult	6	401	0.27 (0.16–0.40)	57
	Outcome measure ≤1 year	7	380	0.43 (0.23–0.64)	74
	Outcome measure >1 year	1	48	0.31 (0.04–0.69)	—
	Industry-funded studies	1	5	0.60 (0.06–1.00)	—
	Non-industry-funded studies	7	423	0.37 (0.21–0.54)	71
	Kidney transplant-only	6	379	0.42 (0.23–0.61)	76
	Kidney-pancreas transplant	2	49	0.36 (0.01–0.83)	49
Persistent ≥Banff Borderline following treatment of subclinical ≥Banff Borderline rejection	Overall	7	133	0.46 (0.28–0.65)	66
	Pediatric	2	38	0.53 (0.26–0.80)	41
	Adult	5	95	0.42 (0.19–0.67)	68
	Outcome measure ≤1 year	7	133	0.46 (0.28–0.65)	66
	Industry-funded studies	2	35	0.51 (0.23–0.79)	0
	Non-industry-funded studies	5	98	0.44 (0.21–0.69)	72
	Kidney transplant-only	6	132	0.45 (0.29–0.62)	69
	Kidney-pancreas transplant	1	1	1.00 (0.00–1.00)	—
Persistent ≥Banff Borderline following treatment of clinical ≥Banff Borderline rejection	Overall	4	302	0.41 (0.19–0.64)	82
	Pediatric	2	14	0.58 (0.18–0.94)	0
	Adult	2	288	0.34 (0.13–0.58)	90
	Outcome measure ≤1 year	4	302	0.41 (0.19–0.64)	82
	Non-industry-funded studies	4	302	0.41 (0.19–0.64)	82
	Kidney transplant-only	4	302	0.41 (0.19–0.64)	82
Persistent ≥Banff Borderline following untreated ≥Banff Borderline rejection	Overall	7	180	0.61 (0.41–0.79)	60
	Pediatric	2	17	0.67 (0.16–1.00)	0
	Adult	5	163	0.58 (0.35–0.80)	70
	Outcome measure ≤1 year	7	180	0.61 (0.41–0.79)	60
	Industry-funded studies	2	18	0.37 (0.10–0.69)	0
	Non-industry-funded studies	5	162	0.70 (0.50–0.88)	48
	Kidney transplant-only	5	37	0.55 (0.27–0.82)	10
	Kidney-pancreas transplant	2	143	0.64 (0.40–0.86)	80

TABLE 3 (Continued)

Outcome	Subgroup	No. of studies	Population size	Pooled proportion (95% CI)	I^2 Statistic (%)
ABMR following treatment of ≥Banff Borderline rejection	Overall	7	488	0.02 (0.00–0.10)	73
	Pediatric	1	28	0.04 (0.00–0.31)	—
	Adult	6	460	0.03 (0.00–0.16)	77
	Outcome measure ≤1 year	5	320	0.02 (0.00–0.16)	54
	Outcome measure >1 year	2	168	0.06 (0.00–0.26)	88
	Industry-funded studies	2	35	0.05 (0.00–0.27)	71
	Non-industry-funded studies	5	453	0.02 (0.00–0.16)	78
	Kidney transplant-only	5	331	0.07 (0.01–0.18)	46
	Kidney-pancreas transplant	2	157	0.00 (0.00–0.13)	85
Graft loss (death censored or not)	Overall	7	427	0.29 (0.03–0.66)	98
	Borderline TCMR	5	282	0.31 (0.01–0.73)	98
	TCMR	3	133	0.55 (0.06–0.98)	90
	Pediatric	1	37	0.14 (0.04–0.27)	—
	Adult	6	390	0.32 (0.02–0.74)	97
	Outcome measure ≤1 year	1	30	0.00 (0.00–0.06)	—
	Outcome measure >1 year	6	397	0.37 (0.06–0.75)	97
	Industry-funded studies	1	30	0.00 (0.00–0.06)	—
	Non-industry-funded studies	6	397	0.37 (0.06–0.75)	97
	Kidney transplant-only	4	167	0.13 (0.00–0.57)	96
	Kidney-pancreas transplant	3	260	0.55 (0.08–0.97)	96
Mortality	Overall	3	242	0.42 (0.00–0.95)	98
	Borderline TCMR	2	119	0.34 (0.00–0.97)	99
	TCMR	2	123	0.72 (0.06–1.00)	84
	Adult	3	242	0.42 (0.00–0.95)	98
	Outcome measure ≤1 year	1	30	0.00 (0.00–0.06)	—
	Outcome measure >1 year	2	212	0.73 (0.48–0.91)	93
	Industry-funded studies	1	30	0.00 (0.00–0.06)	—
	Non-industry-funded studies	2	212	0.73 (0.48–0.91)	93
	Kidney transplant-only	2	118	0.22 (0.00–0.92)	98
	Kidney-pancreas transplant	1	124	0.83 (0.76–0.89)	—

4 | DISCUSSION

Primary alloimmunity remains common in kidney transplant patients on Tac/MPA-based therapy and this study found an incidence of 30% subclinical and 16% clinical ≥Banff Borderline rejection during the first-year posttransplant. The principal finding was that a significant proportion of patients (39%) have persistent ≥Banff Borderline rejection after treatment of an index ≥Banff Borderline rejection and this is even higher in pediatric populations (54%), emphasizing the critical importance of follow-up histology to evaluate remission of rejection. Anti-rejection therapy is foundational to transplant management, however, considerable treatment heterogeneity exists reflecting the dearth of RCTs to define optimal approaches. While pulse steroids and enhanced maintenance immunosuppression are mainstays of TCMR therapy, the low observed histological response rates and known complications of high dose glucocorticoids suggest that improved TCMR management strategies and RCTs evaluating novel drugs for TCMR treatment are urgently required.

By defining TCMR remission using histological criteria, our search criteria are biased to studies that used surveillance/follow-up biopsies. However, subclinical TCMR is a clinically significant BPAR event occurring prior to graft functional decline[30] that predicts transplant failure.[1–6] Subclinical TCMR treatment results in improved histological outcomes.[37,38] Subclinical TCMR is an early independent predictor for *dn*DSA which precedes chronic active ABMR and subsequent graft

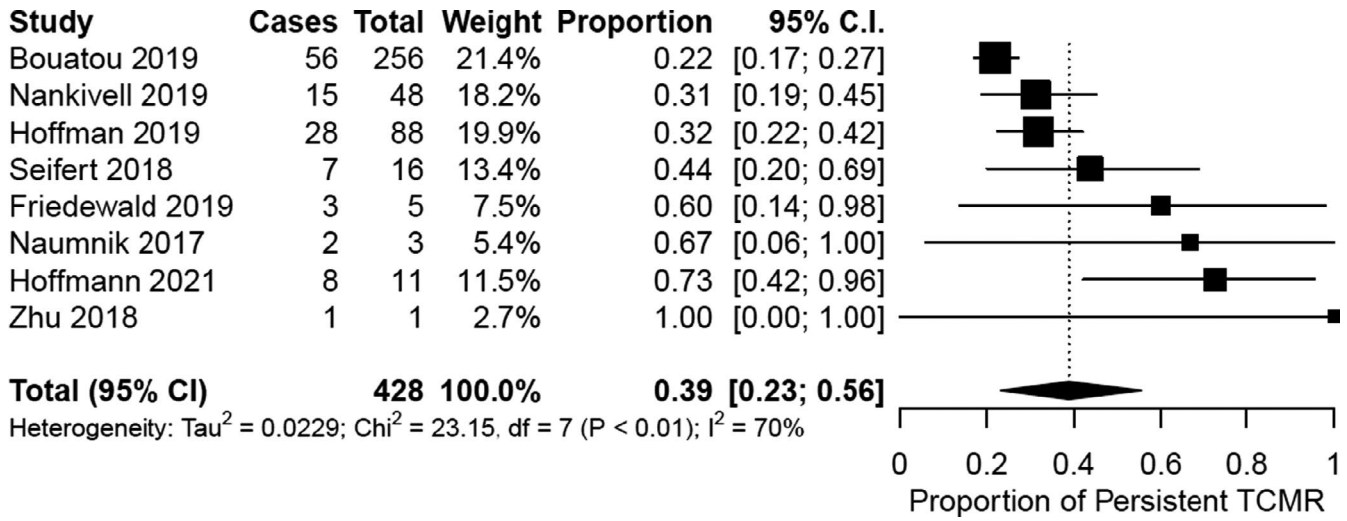


FIGURE 3 Forest plot for persistent ≥Banff Borderline rejection following treatment of ≥Banff 1A rejection

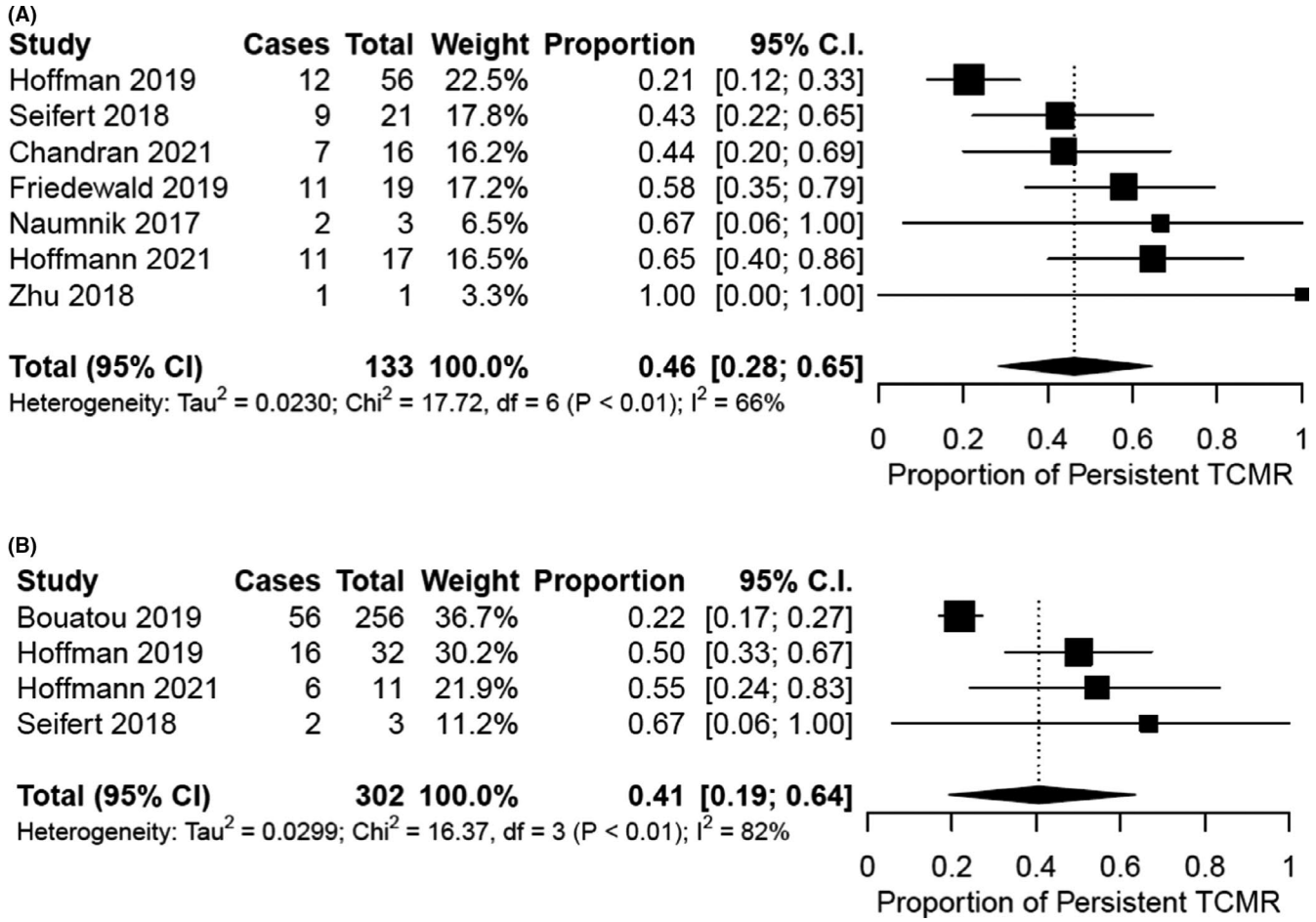


FIGURE 4 (A) Forest plot for persistent ≥Banff Borderline rejection following treatment of subclinical ≥Banff Borderline rejection. (B) Forest plot for persistent ≥Banff Borderline rejection following treatment of clinical ≥Banff Borderline rejection

loss.[39–41] Subclinical and clinical TCMR can lead to graft functional decline and loss in even its "mildest" forms.[1–7,28,30,33] Indeed subclinical Banff Borderline TCMR[7,31,33] or low grades of inflammation which do not meet Banff rejection criteria are independently associated with death-censored graft loss.[42–44] Taken together subclinical and clinical BPAR remains part of the causal pathway leading to graft loss,

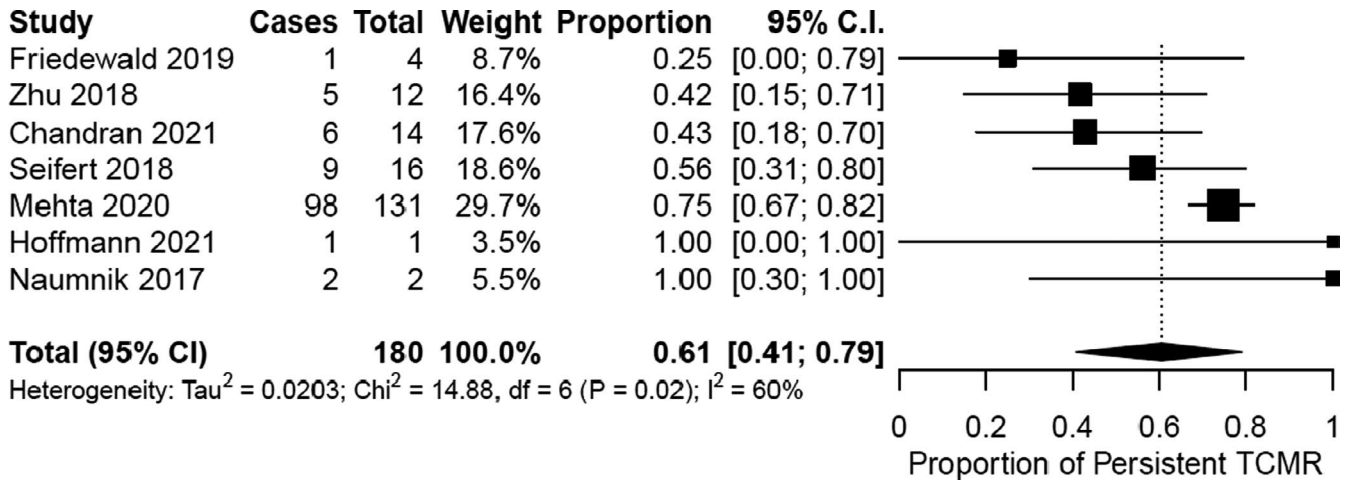


FIGURE 5 Forest plot for persistent ≥Banff Borderline rejection following untreated ≥Banff Borderline rejection

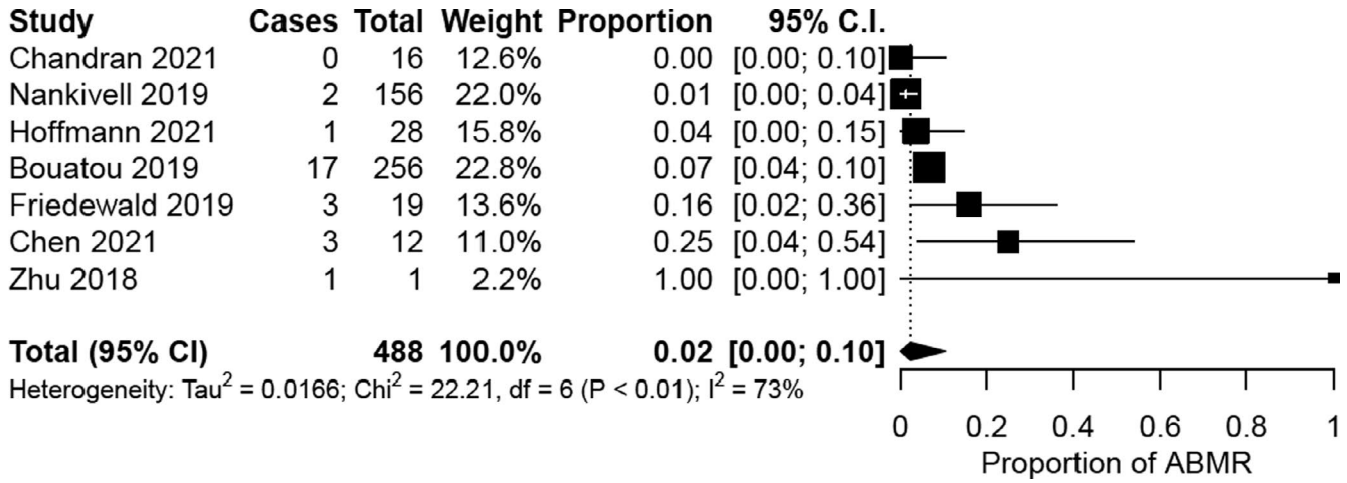
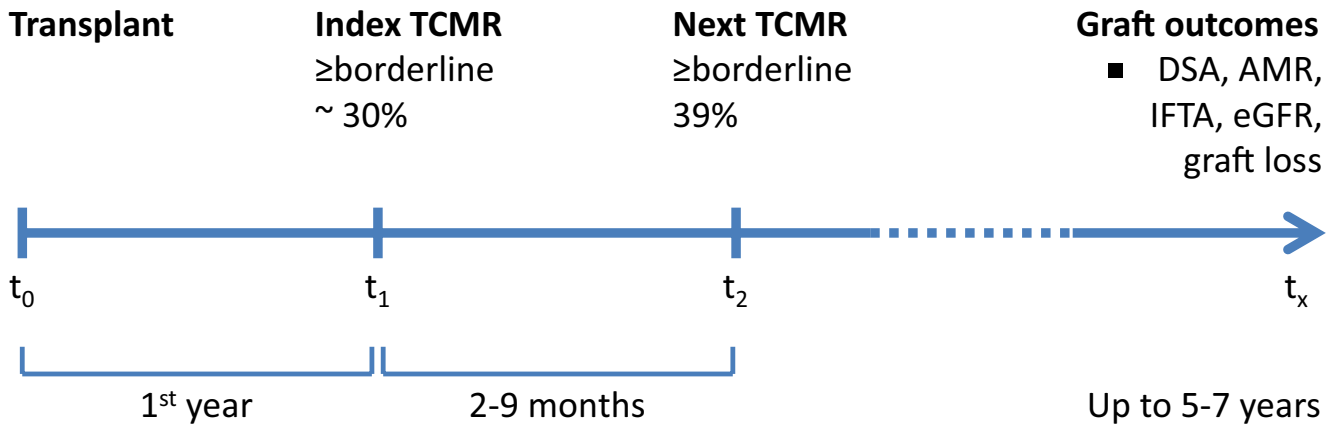


FIGURE 6 Forest plot for ABMR following treatment of ≥Banff Borderline rejection

thus we contend remission of rejection should be histologically defined rather than relying on insensitive graft functional markers such as serum creatinine and/or proteinuria.

We defined histological remission of rejection using <Banff Borderline by the Banff 2005 criteria. It could be argued that the Banff 1997 Borderline definition should be used given its more stringent criteria for the presence of tubulointerstitial inflammation, requiring at least i1.[45] Conversely it could be argued that remission of rejection should be defined as the complete absence of tubulointerstitial inflammation even if it does not meet Banff criteria for rejection. Indeed Mehta et al. elegantly showed that low grades of tubulointerstitial inflammation that do not meet the Banff 1997 or 2005 Borderline definitions remain clinically and prognostically significant,[30] while others have shown that inflammation in areas of atrophy and chronic active TCMR are independently associated with death-censored graft loss.[9,10,42,46] Taken together we classified the histological remission of rejection using Banff rejection criteria to meet FDA-accepted BPAR definitions for RCTs. The Banff 2005 Borderline definition was chosen to include lesser degrees of tubulointerstitial inflammation and allow for more stringency in defining response to therapy. This was supported by an exploratory subgroup analysis restricted to studies which used the 1997 Banff Borderline and found a similar proportion of persistent ≥Banff Borderline (41%) following therapy. Nevertheless this highlights a key knowledge gap in transplantation and the urgent need for a consensus working definition of complete and partial remission of rejection to standardize reporting in the literature and aid in the design of RCTs.

Anti-rejection therapy is foundational to transplant management and standard-of-care for TCMR is considered pulse steroids, but significant practice heterogeneity exists with respect to dose, duration, taper, decision to use thymoglobulin, and inconsistent treatment of Banff Borderline rejection.[11,12,14] Such center-specific practices reflect the lack of robust RCTs to support evidence-based recommendations,[47–49] as well as equipoise with respect to pulse steroid regimens from a clinical trials perspective. High quality observational data for anti-rejection therapy in patients on Tac/MPA-based therapy are also limited.[14] Indeed the extracted outcomes for this systematic review were often not the focus of the included studies



TCMR	TCMR therapy
Subclinical borderline	5/11 no treatment; 6/11 studies: no therapy, ↑maintenance immunosuppression, oral/IV pulse steroids, tocilizumab (variable practices)
Clinical borderline	↑maintenance immunosuppression , oral/IV pulse steroids (variable practices)
Subclinical ≥Banff 1A	Methylprednisolone 250-500mg IV x 3 days, variable taper
Clinical ≥Banff 1A	Methylprednisolone 250-500mg IV x 3 days, variable taper
Steroid resistant	Thymoglobulin IV, variable doses

FIGURE 7 Overview

and outcomes were deduced from the reported data or by correspondence with the authors.

While it might be argued that ongoing inflammation following resolution of graft dysfunction in response to anti-rejection therapy reflects immunological accommodation, the following lines of evidence support the assertion that it is ongoing rejection: (1) Bouatou et al., reported that non-responders to index TCMR treatment show increased *dn*DSA, increased ABMR, and decreased allograft survival[8]; (2) Our group reported that increasing levels of HLA eplet molecular mismatch correlates with persistent TCMR after treatment and that persistent TCMR, independent of ABMR, is associated with both death-censored and all-cause graft loss.[50] Together with the current data this highlights the need to develop safe and more effective approaches to achieve higher rates of remission for early TCMR. Designing a two parallel arm placebo-controlled RCT to determine if a novel TCMR therapy is *superior* to standard-of-care for achieving remission of rejection requires defining the proportion of persistent TCMR group in the active control arm with pulse steroids. This systematic review and meta-analysis synthesized the available literature and provides key data that may be used to inform future RCT design to define the optimal therapeutic approach for TCMR.

The strengths of this study include adherence to known guidelines and standards in the conduct and reporting of the review including having the main search strategy (for MEDLINE) peer reviewed by an independent knowledge synthesis librarian using the PRESS checklist before adapting the strategy for other databases. The literature search was limited to English-language publications and may have excluded any potentially eligible non-English publications. Limiting to kidney/kidney-pancreas transplant patients meant the exclusion of multi-organ transplant studies. Inclusion of kidney-pancreas studies may have added some study heterogeneity, however, the findings remained stable when these studies were excluded. While in some studies it was not clear if all the patients were on Tac/MPA-based therapy, we were able to contact the primary authors on several studies to clarify the data. It is possible, given the study era (2004–2019), that not all follow-up evaluations were sufficiently rigorous to rule-out DSA or ABMR contaminating the assigned diagnosis of persistent TCMR. To determine the frequency of pure persistent TCMR more accurately will require prospective studies. There were slight population differences across the included studies regarding indication for the initial and subsequent biopsies. Therefore these data should be interpreted cautiously in light of the reported study heterogeneity.

5 | CONCLUSION

In summary, there is a high rate of persistent TCMR with 39% of patients having BPAR within 2–9 months of the index TCMR

emphasizing the critical importance of a follow-up biopsy to assess treatment effects. Heterogeneity in anti-rejection treatment reflects a lack of RCTs in patients on Tac/MPA-based therapy. Together, these findings indicate the need for trials designed to address rejection as the entry criteria to develop more efficacious drugs. Such trials require a clinical-pathological definition for persistent TCMR, perhaps with subcategories of complete and partial response. This could be achieved through a new consensus conference of transplant clinicians and pathologists in partnership with regulatory authorities, which was last done in 1995 and relied solely on graft functional improvement to define TCMR resolution.[51]

ACKNOWLEDGMENTS

We thank Angela Osterreicher, MLIS (Neil John Maclean Health Sciences Library, University of Manitoba, Winnipeg Manitoba, Canada) for peer reviewing the Medline search strategy. We also thank Drs. Michael E. Seifert, Dany Anglicheau, Jonathan Chemouny, Chien-Chia Chen, Meng-Kun Tsai, Tom D. Blydt-Hansen, Adam Hoffmann, Rajil Mehta, Patrick Luke, and John Friedewald for responding kindly to our requests for clarifications and additional information.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Peter Nickerson is a consultant with CSL Behring. The other authors declare that they have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Nickerson, Wiebe, and Ho were involved in conceptualization; Nickerson, Okoli, Rabbani, Askin, Rampersad, Trachtenberg, Wiebe, Ho, and Abou-Setta were involved in methodology; Okoli, Lam, and Reddy were involved in data acquisition; Okoli, Rabbani, and Abou-Setta were involved in formal analysis; Nickerson, Okoli, Rabbani, Askin, Rampersad, Trachtenberg, Wiebe, Ho, and Abou-Setta were involved in validation; Nickerson, Okoli, Rabbani, and Abou-Setta were involved in draft manuscript; Nickerson, Okoli, Rabbani, Lam, Reddy, Askin, Rampersad, Trachtenberg, Wiebe, Ho, and Abou-Setta were involved in manuscript revisions; Nickerson, Okoli, Rabbani, Lam, Reddy, Askin, Rampersad, Trachtenberg, Wiebe, Ho, and Abou-Setta were involved in final approval for submission.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ho J, Okoli GN, Rabbani R, et al. Effectiveness of T cell–mediated rejection therapy: A systematic review and meta-analysis. *Am J Transplant*. 2022;22:772–785. doi:10.1111/ajt.16907